Ileal Brake: Neuropeptidergic Control Of Intestinal Transit

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Digestion and absorption of a meal are time-intensive processes. To optimize digestion and absorption, transit of the meal through the gastrointestinal tract is regulated by a complex integration of neuropeptidergic signals generated as the jejunal brake and ileal brake response to nutrients. Mediators involved in the slowing of transit responses include peptide YY (PYY), chemosensitive afferent neurons, intestinofugal nerves, noradrenergic nerves, myenteric serotonergic neurons, and opioid neurons. The activation of this circuitry modifies the peristaltic reflex to convert the intestinal motility pattern from propagative to segmenting. Fat is the most potent trigger of these transit control mechanisms. The integrated circuitry of gut peptides and neurons involved in transit control in response to nutrients is described in this review.

Introduction

Digestion and absorption of a meal are time-demanding events requiring prolonged contact time with bile salts, digestive enzymes, and absorptive mucosa. Precise control of postprandial transit is critical to maintenance of adequate nutrition. The nutrient composition of a meal slows gastric emptying and small intestinal transit to ensure adequate time for complete digestion and absorption, and therefore optimal nutrition. Rapid movement of a meal through the gastrointestinal (GI) tract may reduce hydrolytic and/or absorptive capacity and result in maldigestion or malabsorption. Malabsorption can occur in rapid intestinal transit even if a meal is appropriately digested [1] and the absorptive mucosa is normal. In this setting, nutrients appear in the waste stream instead of the blood stream.

Normal GI motility consists of distinct patterns of neuromuscular contractions, such as peristalsis and segmenting contractions. Whereas peristalsis with propulsion of luminal content would be appropriate in the fasted state, segmenting contractions with mixing and slowing of transit would be appropriate in the fed state. Between meals, upper gut motility is characterized by a cyclical pattern of contractions called the interdigestive or migrating motor complex (MMC) that repeats every 90 to 120 minutes. Phase I of MMC lacks contractile activity; phase II of MMC is a period of intermittent activity; and phase III of MMC is a period of powerful, lumen-obliterating, propagated contractions known as the intestinal housekeeper wave, which moves the luminal content aborally.

After consumption of a meal, peristalsis is inappropriate. Instead, segmenting contractions dominate to mix the content of the intestinal lumen, maximizing access of digestive enzymes to the luminal content and slow intestinal transit to facilitate absorption of digested nutrients. The nutrient content of the meal (type, load, or amount) determines the duration of this fed motility state [2–4]. Nutrient sensors are distributed along the entire length of the intestine to control transit globally in response to specific nutrients. These nutrient sensors represent the integrated neuropeptidergic feedback signals that work together to slow transit in proportion to the nutrient load. This metering effect is achieved when the intensity of inhibitory feedback response is proportional to the length of intestine exposed to the hydrolytic end products of carbohydrates, proteins, and fats [2–5]. As the amount of nutrients exposed to the mucosal surface increases, a greater amount of mucosal surface, and therefore length of the intestine, must participate in absorption. Thus, greater inhibitory feedback is generated in response to a higher nutrient load.

Intestinal Transit Control Mechanisms

In the fasting state, there are no nutrients in the small intestine to generate inhibitory feedback. In the fed state, intestinal transit control mechanisms become activated by the availability of nutrients. During the initial period after ingestion, nutrient-rich chyme surges out of the stomach to distribute nutrients along the length of small intestine. This initial surge determines the intensity of the inhibitory feedback that will control transit of the meal

[2,3,6,7]. The transit control mechanism in the proximal small intestine is known as the jejunal brake [8], and the control mechanism in the distal small intestine is known as the ileal brake [9,10].

Ileal brake

The ileal brake was discovered first. Spiller et al. [10] and Read et al. [9] described the distal transit control mechanism as the "ileal brake" in 1984. Each group separately described slowing of GI transit when the distal gut was perfused with a fat emulsion. Read et al. [9] demonstrated increased orocecal transit time of a non-digestible carbohydrate or of a solid meal in response to triglyceride emulsion but not saline perfused into the ileum 205 cm from the teeth. Spiller et al. [10] showed decreased jejunal motility when partially hydrolyzed triglyceride emulsion (~60-mM free fatty acids) was perfused 170 cm from the teeth.

Jejunal brake

Evidence for a more proximally located transit control mechanism arose from clinical observations made during the same approximate time period as the experiments by Spiller and Read. Woolf et al. [11] reported that fat excretion by patients lacking an ileum remained constant even as their fat intake was increased threefold. Because such increase in fat load would require a much longer assimilation time, keeping the output of stool fat constant would have required slower intestinal transit. A proximal controller known as the jejunal brake was found when oleic acid, an end product of fat digestion, was found to slow intestinal transit even as the fat was confined to the proximal half of the small intestine with no possibility of access to the ileal brake [8].

Jejunal versus ileal brake

When the two transit controllers were directly compared, the ileal brake was found to be more potent than the jejunal brake [12]. This proximal-to-distal graded inhibitory feedback on intestinal transit plays an important role in optimizing nutrient assimilation. As nutrients from a meal surge out of the stomach and spread down the small intestine, they activate the proximal and distal braking mechanisms variably in proportion to the nutrient load. Any nutrients that remain unassimilated within the proximal gut are left to trigger the more potent ileal brake as the meal progresses through the intestine.

However, when the ileum is diseased or missing (eg, Crohn's disease, extensive ileal resection), the jejunal brake becomes the sole remaining transit controller responding to chyme delivered from the stomach. It is thus understandable why the severity of fat malabsorption depends on the region of the small intestine not functioning. When the distal half of the small intestine was removed [13] or taken out of continuity with the proximal half [14••], fecal fat increased from the normal 8% to 10% of ingested amount to 80% to 90%, indicating severe steatorrhea. However, nutrient loss was far less when the proximal 50% to 70% of the small intestine was resected, with fecal fat loss of 15% to 24% [14••]. The more severe steatorrhea in response to removing the distal half of the small intestine can be explained by the loss of the more potent ileal brake, leading to severe loss of controlled intestinal transit.

Nutrient Triggers of Intestinal Brakes

End products of digestion of dietary fat are the most potent trigger of intestinal braking mechanisms. However, dietary protein and carbohydrate are also nutrient triggers of intestinal brakes. Dietary soluble fiber also slows transit, albeit indirectly by extending the spread of nutrients down the length of the intestine to activate the more potent ileal brake response [15•].

Dietary carbohydrate

Gastrointestinal transit and pancreatic amylase secretions increase when the ileum is presented with unhydrolyzed carbohydrate [16–19] but not when the jejunum is presented with glucose as the hydrolyzed carbohydrate [9]. The inhibitory feedback response from the small intestine is maximally triggered by 1M glucose when the nutrient is delivered into the distal-most quartile of the small intestine [18]. Although the luminal content of the small intestine is approximately 300 mOsm by the ligament of Treitz, the greater slowing of gastric emptying of a dinner meal after consumption of a poorly digestible, compared with an easily digestible, starch eaten 4.5 hours earlier, suggests that complex carbohydrates normally escape assimilation by the proximal intestine to reach the ileum [18,19].

Dietary protein

Intestinal transit time increases in proportion to the protein content of a meal [4] to allow assimilation of the greater protein load. The intensity of this inhibitory feedback depends on contact between proteolytic end products and the intestinal nutrient sensors that trigger slowing. Whereas protein hydrolysis increases absorption to limit the number of sensors recruited for inhibitory feedback, intact protein remains in the lumen longer to trigger greater feedback [20].

Dietary fat

Dietary lipids initiate a feedback reflex that converts the propagative to the non-propagative motility pattern that characterizes the fed state [21,22]. Many diverse lipid substances are capable of activating the ileal brake, including triglycerides, phospholipids, and long- and short-chain non-esterified fatty acids (NEFA) [23,24], requiring lipase activity [24]. Of the three macronutrients, dietary fat most potently slows GI transit [2–4,9,20]. Fat entering the small intestine is also the most potent trigger of the reflexive stimulation of a colonic mass movement known as the gastrocolonic reflex.

Dietary fiber

Inclusion of dietary fiber in an enteral formula decreases the incidence of diarrhea [25,26], suggesting that digestion and absorption are improved with the treatment. Dietary fiber modifies GI transit time dependent on fiber type, with water-soluble fibers generally slowing transit and water insoluble fibers generally accelerating transit [27]. Intestinal feedback is intensified by feeding a water-soluble fiber-containing formula [28], which causes nutrients to be spread further down the intestine to recruit the more potent ileal brake response. Specifically, with the addition of water-soluble fiber, the rate of nutrient absorption is slowed as the unstirred layer is thickened. This effect would delay the removal of nutrients from the intestinal lumen, resulting in the presentation of nutrients further and further down the length of the small intestine [15•].

Clinical relevance: tube feeding–induced diarrhea

Successful enteral feeding is achieved when the goal of delivering calories is met without the triggering of an adverse effect, such as diarrhea [20]. Tube feeding induces diarrhea in up to two thirds of patients on enteral support [29]. In an effort to decrease diarrhea, the rate of delivery is often decreased, resulting in diminished nutrient delivery to the patient. This strategy is often erroneously followed based on the view of the intestine as a garden hose in which transit is determined only by flow rate. Significant decrease in the frequency of diarrhea can be achieved by adding soluble fiber to an enteral formula [30]. With the addition of soluble fiber, increasing rather than the usual response of decreasing the delivery rate of the enteral feeding would slow intestinal transit by spreading a higher load of nutrients down a longer length of intestine to trigger the more potent ileal brake in the distal small intestine [28].

Clinical relevance: short bowel syndrome

In short bowel syndrome (patients with less than 100 cm proximal intestine remnant), loss of the ileocecal sphincter and the ileal brake due to resection accelerates transit of an oral meal through the entire length of the GI tract. Rapid transit, coupled with reduced absorptive surface area, leads to malnutrition and often life-long dependence on parenteral nutrition. A nutritional approach that does not rely on distal braking is required to limit the chronic problems of postprandial diarrhea, bloating, nausea, and abdominal pain these patients experience. Because the efficiency of protein absorption in the absence of ileal brake triggers depends not on load but on hydrolytic state [19], enteral formulas containing partially or completely hydrolyzed proteins have been used successfully to maintain some short bowel syndrome patients with enteral nutrition. This strategy was used to maintain a pediatric patient with only 8 cm of proximal jejunum and 5 cm of terminal ileum on an elemental diet, resulting in normal growth and development [31].

Neuropeptidergic Mechanisms of Intestinal Brakes

The mechanisms that underlie the jejunal and ileal brake can be described as a reflex response that contains an afferent (nutrient sensing) limb in the distal gut and an efferent (transit regulating) limb in the proximal gut. In a dog model equipped with a duodenal and a mid-intestinal fistula, the proximal versus distal half of small intestine was compartmentalized with occluding Foley catheters placed in the distal limb of each fistula. To test the fat-induced ileal brake, the distal half of gut was perfused with fat, triggering an intestine-intestinal inhibitory feedback to slow the transit of buffer that was perfused across the proximal half of gut. Using this model, the distal gut represented the afferent limb and the proximal gut represented the efferent limb.

Afferent limb–distal gut

Conversion of nutrient sensing to transit braking requires a nutrient-sensitive mucosal afferent nerve. Submucosal nerves that respond to luminal fat have been characterized previously when direct recording from the vagus nerve showed that selected nerve fibers respond to luminal fat but not other nutrients to demonstrate their role as fat-sensitive chemoreceptive nerves [32,33]. The role of nutrient-sensing mucosal nerve has been tested with the mucosal anesthetic oxethazaine [34]. Using this approach, the ileal brake was shown to be dependent on a chemosensitive afferent nerve when oxethazaine blocked the fat-induced ileal brake response [35].

Because fat in the intestinal lumen is separated from the mucosal afferent nerve endings by intestinal mucosa, a signal transducer, such as a gut peptide, is needed to carry the signal across the epithelial barrier. Cells that release gut peptides are regionally located, with cholecystokinin (CCK)-releasing cells positioned primarily in the proximal gut and peptide YY (PYY)-releasing L cells positioned primarily in the distal gut. PYY immunoreactive cells are found in large numbers in the ileum and colon but not in the duodenum or jejunum. PYY is coexpressed with glucagon-like peptide 1 (GLP-1) by enteroendocrine cells known as L cells [36]. PYY is a natural candidate signal transducer for the fat-induced ileal brake because L cells primarily populate the ileum and colon and PYY is released most strongly by fat [36]. The role of PYY as a gut peptide mediator of the ileal brake response was demonstrated by showing that fat-induced ileal brake was abolished by PYY immunoneutralization [37]. In addition, the afferent nerve endings described previously are co-localized with the PYY-releasing L cells in the terminal ileum [38], suggesting a direct connection between chemoreceptive neurons and neuropeptide hormone release by the distal gut.

PYY has a similar role in the jejunal brake response to fat, as immunoneutralization of PYY also abolished the slowing of intestinal transit by fat confined to the proxi-

mal gut [39]. This is possible because the release of distal gut PYY by fat in either the proximal or distal gut is similar [40]. The possibility that CCK could be the foregut signal to the distal gut L cells was suggested by studies that showed PYY release in response to either intravenously administered CCK [41] or orally administered oil [42]. While confining fat to the proximal half of the small intestine, PYY release was attenuated by pretreatment with either a CCK-A receptor antagonist [42,43] or a cholinergic antagonist [44,45] to demonstrate the role of CCK and a cholinergic neuron in the release of PYY from the distal gut by fat in the proximal gut.

Taken together, these studies suggest a model in which jejunal fat causes CCK-secreting cells in the proximal gut to release CCK into the circulation. Circulating CCK binds to CCK-A receptors in distal enteric neurons [46,47,48•], causing the release of acetylcholine [49–51], which releases PYY and slows intestinal transit. Mucosal anesthetic also abolishes slowing of intestinal transit by intravenously administered PYY to demonstrate that fat slows intestinal transit via PYY stimulation of a chemosensitive afferent pathway [52] that may be intrinsic to the intestine [53•]. There are two possible arrangements for a fat- and PYY-sensitive mucosal afferent nerve:

1. a PYY-sensitive intrinsic primary afferent neuron (IPAN) that synapses with an intestinofugal nerve carrying the slowing signal from the intestine to a prevertebral ganglion; and

2. an extrinsic vagal or spinal sensory nerve that expresses 5-hydroxytryptamine (5-HT; serotonin) type 3 (5-HT_3) receptors [54,55] that carries the signal from the intestine to the central nervous system (CNS) with a branch to a prevertebral ganglion.

A PYY-sensitive IPAN-intestinofugal nerve is the more attractive choice for conveying the fat signal from the afferent limb because the density of intestinofugal nerves increases going from jejunum to ileum [56], matching the greater potency of the ileal brake compared with the jejunal brake [12].

Efferent limb–proximal gut

Enterochromaffin cells in the luminal mucosa sample the luminal content and release serotonin into the lamina propria in response to nutrients [57]. The three main known neuronal types in the intestine that respond to serotonin are the mechanosensitive IPAN, extrinsic sensory afferent nerves, and serotonin-synthesizing and -releasing neurons in the myenteric plexus. The mechanosensitive IPAN responds to mucosal serotonin or 5-HT via 5-HT_4 receptors to modulate intestinal secretion and the peristaltic reflex [58,59]. Extrinsic sensory nerves communicate from intestine to the CNS via 5-HT_3 receptors [54,60,61]. The 5-HT synthesizing and releasing myenteric neurons abut neighboring motoneurons expressing 5-HT_3 receptors to suggest their role as interneurons on the efferent limb of a reflex. The physiologic function of these myenteric neurons was previously unknown.

The role for a serotonergic pathway located on the efferent limb of the fat-induced ileal brake was shown when the 5-HT_3 receptor antagonist ondansetron abolished the slowing of intestinal transit when perfused into the proximal gut (efferent limb of the reflex) but had no effect when perfused into the distal gut (afferent limb of the reflex) [62•]. By matching the efferent location with the involvement of 5-HT_3 receptors, the site of this serotonergic pathway was localized to 5-HT neurotransmission via myenteric neurons. This role for the myenteric 5-HT synthesizing neurons as the source of the 5-HT was further tested with 5,7-dihydroxytryptamine (5,7-DHT), a neurotoxin selective for peripherally located serotonergic neurons. Following treatment with 5,7-DHT, the ileal brake was abolished [63•] to demonstrate slowing of intestinal transit as the physiologic role of myenteric 5-HT neurons. Transit is then modified in a site-specific fashion. Although mucosal 5-HT acting on 5-HT_4 or 5-HT_1p receptors in the peristaltic reflex is generally considered the action of enteric 5-HT, neuronal 5-HT also participates in 5-HT_3 receptor-dependent neurotransmission. These opposing effects of enteric serotonin may be relevant to our understanding of the GI side effects of such medications as the serotonin reuptake inhibitors (SSRI) and serotonin receptor directed agonist and antagonists used in treating such conditions as irritable bowel syndrome.

Dichotomy: effect of 5-HT in in vitro versus in vivo experiments

Luminal perfusion with 5-HT slowed intestinal transit in a dose-dependent fashion [62•], demonstrating that the effect of serotonin on intestinal transit in the whole animal is opposite to that seen in in vitro experiments where the anticipated effect of 5-HT is acceleration of transit via the peristaltic reflex [58]. Because extrinsic nerves are severed in in vitro experiments, a comparison of these effects of serotonin would point to the need for extrinsic nerves in the slowing of transit response, an intestine-intestinal reflex response that would allow fat in the distal gut to slow transit at a distance across the proximal gut. A potential neuronal circuitry was suggested by the nerves involved in the inhibition of one segment of the intestine by mechanical stimulation of another [63•]. In this reflex response, a cholinergic afferent takes the signal out of the intestine by projecting to a prevertebral ganglion, where it synapses with a noradrenergic efferent nerve that carries the signal back to the intestine. Using the nonspecific β-adrenergic receptor (β-AR) antagonist propranolol, the role of a noradrenergic nerve in the fat-induced ileal brake was confirmed when this blocker abolished the ileal brake. In addition, metoprolol (specific β1-AR antagonist) but not phenotolamine (α-AR antagonist) reversed fat- or PYY-mediated

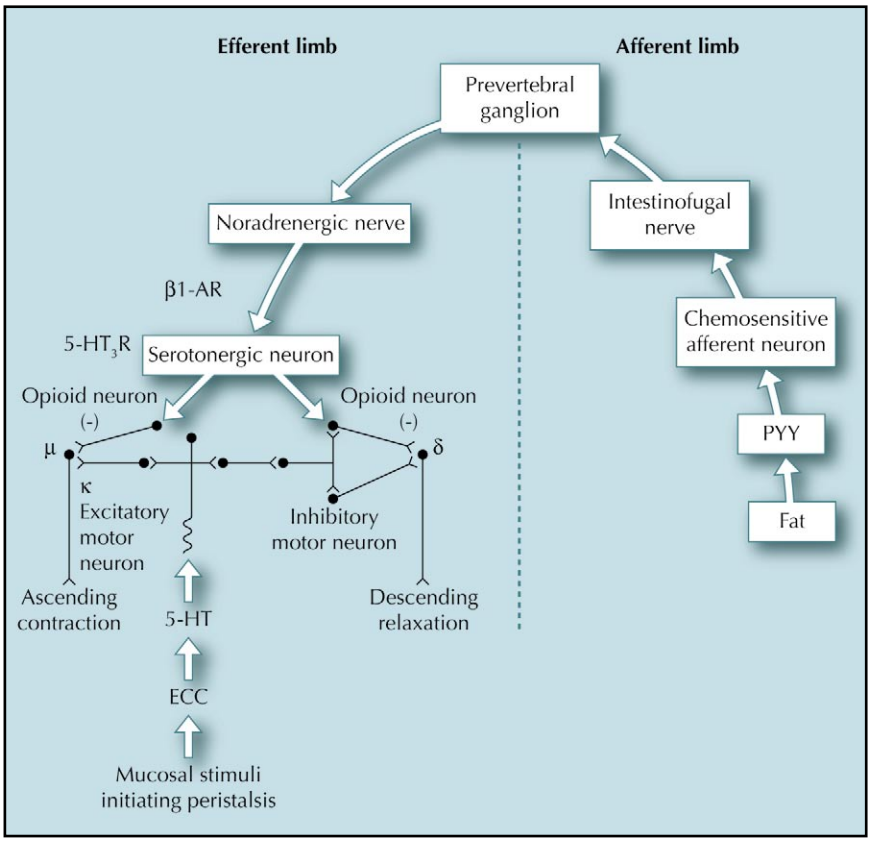

Figure 1. This schematic drawing shows the neuropeptidergic circuitry for the fat-induced jejunal brake and ileal brake as suggested by mostly physiologic experimental results. The afferent and efferent limb of the slowing reflex are separated by the *dotted line*. The reflex begins on the afferent limb of the reflex response, consisting of fat, peptide YY (PYY), chemosensitive afferent neuron, and an intestinofugal nerve, and ends on the efferent limb of the reflex response, consisting of the noradrenergic nerve, myenteric serotonergic neurons (5-HT), and opioid interneurons that inhibit the peristaltic reflex. β1-adrenoreceptors (β1-AR) are postulated to be expressed by myenteric serotonergic neurons. 5-HT_3 receptors (5-HT_3R) are postulated to be expressed by opioid interneurons. ECC—enterochromaffin cells.

slowing [64] to suggest the role for β1-AR. The role of a noradrenergic nerve was further supported by the finding of β1-AR immunoreactivity in selected neurons of the myenteric plexus. This noradrenergic pathway was linked with the previously shown serotonergic pathway by showing that the slowing of intestinal transit by norepinephrine was abolished by the 5-HT_3 antagonist ondansetron [65•]. It is likely that these two mediators on the efferent limb of the reflex are linked through the expression of β-adrenergic receptor by myenteric 5-HT interneurons.

Slowing of intestinal transit by endogenous opioid pathway

Opioid immunoreactive fibers are found throughout the enteric nervous system [66], but their physiologic role in regulating transit was previously limited to their involvement in the slowing of intestinal transit in response to exogenously administered opioids. Perfusion of the proximal but not distal small intestine with naloxone, a nonspecific opioid receptor antagonist, during fat perfusion of the distal intestine abolishes the fat-triggered ileal brake efferent pathway to demonstrate the role of an opioid pathway located on the efferent limb of the slowing reflex. Similarly, luminal naloxone reversed the slowing of intestinal transit by PYY, norepinephrine, or serotonin [67•] to localize the opioid pathway in the proposed control circuitry beyond these mediators. Naloxone also abolishes the fat-triggered jejunal brake to demonstrate the crucial role of endogenous opioids in both of these gut transit controllers [68]. Because μ, κ, and δ opioid receptors are expressed by interneurons that modulate the peristaltic reflex, slowing of intestinal transit in response to fat appears to activate a sequence of events that ultimately results in the activation of opioid pathways altering the peristaltic reflex in favor of the more chaotic, segmenting pattern of contractions characteristic of the fed motility state. Superior slowing of intestinal transit could therefore be achieved by physiologically engaging all three opioid receptors, as in the setting of fat-triggered ileal brake, compared with engaging only the μ receptors in the case of exogenous opioids, such as loperamide or opium.

Conclusions

Intestinal transit is slowed by nutrients to permit sufficient time of residence of food in the small intestine for optimal assimilation. Fat is the most potent trigger of this feedback response on intestinal transit. There are two transit control mechanisms in the small intestine, the jejunal brake and the ileal brake. These braking controllers operate as a reflex response consisting of an afferent limb that senses luminal fat and an efferent limb that slows intestinal transit (Fig. 1). Current evidence, drawn mostly from physiologic experiments with limited direct neuronal mapping, suggests that this feedback reflex depends on the integrated action of a neuropeptidergic circuitry that involves, on the afferent limb, the sequential activation by luminal fat of PYY, a mucosal chemosensitive

afferent neuron and an intestinofugal nerve that takes the signal out of the intestine and projects to a prevertebral ganglion. There, the intestinofugal nerve synapses with a noradrenergic nerve that takes the signal back to the intestine by projecting to myenteric serotonergic neurons that express β1-adrenoreceptors. Thus, on the efferent side, norepinephrine initiates serotonergic neurotransmission. Neuronal 5-HT acts then on 5-HT_3 receptors expressed by opioid interneurons, inhibiting the excitatory and inhibitory motor neurons that are involved in the peristaltic reflex. These opioid interneurons link fed and fasting motility by inhibiting ascending contraction to decrease motility and by inhibiting descending relaxation to increase motility. Thus, in response to nutrients, this circuitry is activated to change intestinal motility from the propagative contractions of peristalsis of the fasted state to the chaotic and nonpropagative pattern that slows intestinal transit in the fed state.

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